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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/619,047	07/19/2000	Jay Leng	CHEM1110	1555

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EXAMINER

PAK, YONG D

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 04/16/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Applicant(s)

09/619,047

Applicant(s)

LENG, JAY

Examiner

Yong Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 January 2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1 and 3-65 is/are pending in the application.
- 4a) Of the above claim(s) 9-65 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 6-8 is/are rejected.
- 7) ☒ Claim(s) 4 and 5 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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### **DETAILED ACTION**

The amendment filed on January 12, 2002, canceling claim 2 and amending claims 1 and 3, has been entered.

Claims 1 and 3-65 are pending.

The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous Office action are hereby withdrawn.

### ***Election/Restrictions***

Claims 9-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No.16.

### ***Claim Rejections - 35 USC § 112***

Claims 1, 3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the luciferase of SEQ ID NO: 2 substituted with a recognition site at residues 197-200, does not reasonably provide enablement for luciferases different from SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Despite knowledge in the art for the isolation of amino acids, the specification fails to provide guidance regarding how to isolate other *Renilla* luciferase whose sequence is different from SEQ ID NO:2. Therefore, the breadth of these claims is much larger than the scope enable by the specification.

The predictability as to the level of conservation between the disclosed sequences and those of other *Renilla* luciferase is complex. While recombinant techniques are available, it is not routine in the art to screen large numbers of amino acids where the expectation of obtaining similar sequences is unpredictable. The amino acid sequence determines the structural and functional properties of an enzyme. Knowledge of which sequences can be altered or removed and still result in similar protein activity is well outside the realm of routine experimentation.

Therefore, one of ordinary skill would require guidance in order to make luciferase of SEQ ID NO: 2 substituted with a recognition site at residues 197-200 in a manner reasonable correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

***Claim Rejections - 35 USC § 102***

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Korant et al.

Korant et al. teach a *Renilla* luciferase cleavable by a protease, wherein cleavage results in a decrease in luciferase activity (abstract, page 520 and pages 520-521). Therefore, the teachings of Korant et al. anticipates claim 1.

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korant et al. in view of Xu et al.

Korant et al. teach a *Renilla* luciferase cleavable by a protease, wherein cleavage results in a decrease in luciferase activity, as discussed above. This result was then incorporated into a rapid, sensitive and quantitative assay for HIV protease activity (abstract, page 520 and pages 521-523).

The difference between the reference of Korant et al. and the instant invention is that the reference of Korant et al. does not teach a luciferase having the recognition and cleavage site of caspase-3.

Xu et al. teach that the recognition and cleavage site of caspase-3 is DEVD (page 2034, 3<sup>rd</sup> paragraph) and that caspase-3 is activated during cell death (page 2034, 3<sup>rd</sup> paragraph). Xu et al. teach detection of caspase-3 activity during cellular apoptosis with a marker protein, a green fluorescent protein (page 2034).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a *Renilla* luciferase substituted with a recognition site of caspase-3, DEVD. The motivation of substituting DEVD into a

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luciferase, a marker protein like GFP, is to detect caspase-3 activity during apoptosis by monitoring luminescence given off by luciferase. One of ordinary skill in the art would have had a reasonable expectation of success since short peptides are successfully substituted into a polypeptide and luciferases are routinely used in monitoring proteins.

### ***Response to Arguments***

Applicant's arguments filed January 12, 2002 have been fully considered but they are not persuasive.

### ***Claim Rejections - 35 USC § 112***

Claims 1, 3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that a *Renilla* luciferase cleavable by a protease, wherein cleavage results in a decrease in luciferase activity meets the written description requirement (Remarks, page 4, 3<sup>rd</sup> paragraph). The examiner disagrees.

Even though the claim limits the source of the luciferase to the family of *Renilla* luciferases, these claims are still drawn to a genus of polypeptides of unlimited structure described by the function of having a decrease luciferase activity upon cleavage by a protease. The specification only describes SEQ ID NO:2, a luciferase from *Renilla reniformis*, substituted with a recognition site at residues 197-200 wherein cleavage by

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a caspase-family protease decreases luciferase activity. A description of only one type of *Renilla* luciferase modified with several recognition sites out of a diverse genus of polypeptides is not representative of the species that have different structures but the same function. Therefore, the specification fails to describe other representative species by identifying characteristics or structural properties other than the functionality of being a polypeptide cleavable by a protease, wherein cleavage results in a decrease in luciferase activity.

***Claim Rejections - 35 USC § 103***

Claims 1-3 and 6-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lorenz et al. in view of Xu et al.

Applicants argue that the reference of Xu et al. does not teach nor suggest use of a luciferase sequence nor addition of DEVD into any protein to monitor the presence of caspase-3. Although Xu et al. do not directly teach use of a luciferase with a DEVD cleavage site to monitor the activity of caspase-3, one of ordinary skill in the art would have had motivation to use other fluorescent or bioluminescent protein markers, such as a luciferase. Lorenz et al. teach that luciferases are efficient marker proteins (Office Action, Paper No. 17).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a *Renilla* luciferase substituted with a recognition site of caspase-3, DEVD.

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***Allowable Subject Matter***

Claims 4-5 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 703-308-9363. The examiner can normally be reached on 8:00 A.M. to 4:30 P.M weekdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9310 for regular communications and 703-746-7240 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Yong Pak  
Patent Examiner

April 9, 2002



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